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Application of: Dai *et al.*

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Examiner: James Martinell

For: CLASSIFICATION OF BREAST CANCER PATIENTS USING A COMBINATION OF CLINICAL CRITERIA AND INFORMATIVE GENESETS

Attorney Docket No: 9301-251-999 (CAM No.: 301891-999242)

RESPONSE TO SECOND RESTRICTION REQUIREMENT WITH TRAVERSE AND THIRD PRELIMINARY AMENDMENT UNDER 37 C.F.R. 1.115

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

Pursuant to 37 C.F.R. § 1.115 and in response to the Office Action mailed on August 19, 2009 in connection with the above-identified application, please enter the following amendments and consider the following remarks. Applicants submit concurrently herewith a Petition for Extension of Time and an Amendment Fee Transmittal, accompanied by the appropriate fees.

Amendments to the Claims are reflected in the listing of the claims which begins on page 2 of this paper.

Remarks begin on page 10 of this paper.

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application.

1-28. (Cancelled).

29. (Currently Amended) A method for assigning an individual having breast cancer to one of a plurality of categories in a clinical trial, comprising:

(a) classifying said individual as ER^-, *BRCA1*[[,]]; ER^-, sporadic; ER+, ER/AGE high; ER+, ER/AGE low, LN+; or ER+, ER/AGE low, LN^-, wherein ER+ designates a high ER level and ER- designates a low ER level, wherein said ER/AGE is a metric of said ER level relative to the age of said individual, and wherein LN+ designates a greater than 0 lymph nodes status in said individual and LN- designates a 0 lymph nodes status in said individual;

(b) determining for said individual a profile comprising measurements of the ~~level~~ levels of expression of at least two respective genes for which markers are listed in

(b1) Table 1 if said individual is classified as ER^-, sporadic;

(b2) Table 2 if said individual is classified as ER^-, *BRCA1*;

(b3) Table 3 if said individual is classified as ER+, ER/AGE high;

(b4) Table 4 if said individual is classified as ER+, ER/AGE low, LN+; or

(b5) Table 5 if said individual is classified as ER+, ER/AGE low, LN^-;

(c) classifying ~~determining~~, on a computer, said individual as having a good prognosis or a poor prognosis by a method comprising comparing said profile to a good prognosis template and/or a poor prognosis template, wherein:

(i) said individual is classified as having a good prognosis if said profile has a high similarity to said good prognosis template, has a low similarity to said poor prognosis template, or has a higher similarity to said good prognosis template than to said poor prognosis template, wherein said profile has a high similarity to said good prognosis template if the similarity to said good prognosis template is above a predetermined threshold, or has a low similarity to said poor prognosis template if the similarity to said poor prognosis template is below said predetermined threshold, or

(ii) said individual is classified as having a poor prognosis if said profile has a high similarity to said poor prognosis template, has a low similarity to said good prognosis template, or has a higher similarity to said poor prognosis template than to said good prognosis template, wherein said profile has a high similarity to said poor prognosis template

if the similarity to said poor prognosis template is above said predetermined threshold, or has a low similarity to said good prognosis template if the similarity to said good prognosis template is below said predetermined threshold,

wherein said good prognosis template comprises measurements of the levels of expression of said at least two respective genes that are representative of levels of expression of said at least two respective genes in a plurality of good outcome patients, and said poor prognosis template comprises measurements of the levels of expression of said at least two respective genes that are representative of levels of expression of said at least two respective genes in a plurality of poor outcome patients, and wherein a good outcome patient is a breast cancer patient who has non-reoccurrence of metastases within a first period of time after initial diagnosis and a poor outcome patient is a patient who has reoccurrence of metastases within a second period of time after initial diagnosis ~~whether said individual has a pattern of expression of said at least two genes that correlates with a good prognosis or a poor prognosis~~; and

(d) assigning said individual to one category in a clinical trial if said individual ~~has a~~ is classified as having a good prognosis, and assigning said individual to a second category in said clinical trial if said individual ~~has a~~ is classified as having a poor prognosis.

30-41. (Canceled)

42. (Currently Amended) A method for predicting a breast cancer patient as having a good prognosis or a poor prognosis, comprising:

(a) classifying said breast cancer patient into one of the following classes: (a1) ER^-, sporadic; (a2) ER^-, *BRCA1*; (a3) ER+, ER/AGE high; (a4) ER+, ER/AGE low, LN+; or (a5) ER+, ER/AGE low, LN^-;

(b) determining a profile comprising measurements of levels of transcripts of, or proteins encoded by, respective genes in a plurality of genes in a cell sample taken from said breast cancer patient, said ~~plurality of~~ respective genes comprising at least two of the genes for which markers are listed in

(b1) Table 1 if said breast cancer patient is classified as ER^-, sporadic;

(b2) Table 2 if said breast cancer patient is classified as ER^-, *BRCA1*;

(b3) Table 3 if said breast cancer patient is classified as ER+, ER/AGE high;

(b4) Table 4 if said breast cancer patient is classified as ER+, ER/AGE low, LN+; or

(b5) Table 5 if said breast cancer patient is classified as ER+, ER/AGE low, LN^-; and

(c) comparing ~~classifying~~, on a computer, said profile to a good prognosis template and/or a poor prognosis template, wherein said good prognosis template comprises measurements of levels of transcripts of, or proteins encoded by, said respective genes in said plurality of genes that are representative of levels of transcripts of, or proteins encoded by, said respective genes in a plurality of good outcome patients, and said poor prognosis template comprises measurements of levels of transcripts of, or proteins encoded by, said respective genes in said plurality of genes that are representative of levels of transcripts of, or proteins encoded by, said respective genes in a plurality of poor outcome patients, and wherein a good outcome patient is a breast cancer patient who has non-reoccurrence of metastases within a first period of time after initial diagnosis and a poor outcome patient is a patient who has reoccurrence of metastases within a second period of time after initial diagnosis; and

(d) classifying said breast cancer patient (i) as having a good prognosis if said profile has a high similarity to said good prognosis template, has a low similarity to said poor prognosis template, or has a higher similarity to said good prognosis template than to said poor prognosis template, wherein said profile has a high similarity to said good prognosis template if the similarity to said good prognosis template is above a predetermined threshold, or has a low similarity to said poor prognosis template if the similarity to said poor prognosis template is below said predetermined threshold, or (ii) as having a poor prognosis if said profile has a high similarity to said poor prognosis template, has a low similarity to said good prognosis template, or has a higher similarity to said poor prognosis template than to said good prognosis template, wherein said profile has a high similarity to said poor prognosis template if the similarity to said poor prognosis template is above said predetermined threshold, or has a low similarity to said good prognosis template if the similarity to said good prognosis template is below said predetermined threshold, ~~based on said profile of said plurality of genes,~~

wherein ER^+ designates a high ER level and ER^- designates a low ER level, wherein said ER/AGE is a metric of said ER level relative to the age of said patient, and wherein LN^+ designates a greater than 0 lymph nodes status in said patient and LN^- designates a 0 lymph nodes status in said patient.

43-44. (Canceled).

45. (Currently Amended) The method of ~~claim 43~~ claim 42, wherein said profile is an expression profile comprising measurements of said levels ~~a plurality~~ of transcripts ~~in a~~

~~sample derived from said patient~~, wherein said good prognosis template comprises measurements of ~~said plurality~~ levels of transcripts of said respective genes that are representative of expression levels of said transcripts in said plurality of good outcome patients, and wherein said poor prognosis template comprises measurements of ~~said plurality~~ levels of transcripts of said respective genes that are representative of expression levels of said transcripts in said plurality of poor outcome patients.

46-47. (Canceled).

48. (Currently amended) The method of claim 45, wherein measurement of each said transcript in said good prognosis template is an average of expression levels of said transcript in said plurality of good outcome patients, and wherein measurement of each said transcript in said poor prognosis template is an average of expression levels of said transcript in said plurality of poor outcome patients.

49-53. (Canceled)

54. (Previously presented) The method of claim 42, wherein said ER/AGE is classified as high if said ER level is greater than $c\cdot(\text{AGE} - d)$, and wherein said ER/AGE is classified as low if said ER level is equal to or less than $c\cdot(\text{AGE} - d)$, wherein c is a coefficient, AGE is the age of said patient, and d is an age threshold.

55-57. (Canceled).

58. (Previously presented) The method of claim 42, wherein said individual is ER^-, sporadic, and said plurality of genes comprises at least two of the genes for which markers are listed in Table 1.

59. (Previously presented) The method of claim 42, wherein said individual is ER^-, sporadic, and said plurality of genes comprises all of the genes for which markers are listed in Table 1.

60. (Previously presented) The method of claim 42, wherein said individual is ER^-, *BRCA1*, and said plurality of genes comprises at least two of the genes for which markers are listed in Table 2.

61. (Previously presented) The method of claim 42, wherein said individual is ER^-, *BRCA1*, and said plurality of genes comprises all of the genes for which markers are listed in Table 2.

62. (Original) The method of claim 42, wherein said individual is ER+, ER/AGE high, and said plurality of genes comprises at least two of the genes for which markers are listed in Table 3.

63. (Original) The method of claim 42, wherein said individual is ER+, ER/AGE high, and said plurality of genes comprises all of the genes for which markers are listed in Table 3.

64. (Original) The method of claim 42, wherein said individual is ER+, ER/AGE low, LN+, and said plurality of genes comprises at least two of the genes for which markers are listed in Table 4.

65. (Original) The method of claim 42, wherein said individual is ER+, ER/AGE low, LN+, and said plurality of genes comprises all of the genes for which markers are listed in Table 4.

66. (Previously presented) The method of claim 42, wherein said individual is ER+, ER/AGE low, LN^-, and said plurality of genes comprises at least two of the genes for which markers are listed in Table 5.

67. (Previously presented) The method of claim 42, wherein said individual is ER+, ER/AGE low, LN^-, and said plurality of genes comprises all of the genes for which markers are listed in Table 5.

68-88. (Canceled).

89. (Currently Amended) A computer-implemented method for predicting a breast cancer patient as having a good prognosis or a poor prognosis, comprising:

classifying, on a computer, said patient as having a good prognosis or a poor prognosis based on a profile comprising measurements of levels of transcripts of, or proteins encoded by, respective genes in a plurality of genes in a cell sample taken from said patient, said plurality of genes comprising at least two of the genes for which markers are listed in

(b1) Table 1 if said patient has been classified as ER^-, sporadic;

(b2) Table 2 if said patient has been classified as ER^-, *BRCA1*;

(b3) Table 3 if said patient has been classified as ER+, ER/AGE high;

(b4) Table 4 if said patient has been classified as ER+, ER/AGE low, LN+; or

(b5) Table 5 if said patient has been classified as ER+, ER/AGE low, LN^-,

wherein ER^+ designates a high ER level and ER^- designates a low ER level, wherein said ER/AGE is a metric of said ER level relative to the age of said patient, ~~and wherein~~ wherein LN^+ designates a greater than 0 lymph nodes status in said patient and LN^- designates a 0 lymph nodes status in said patient,

wherein said classifying is carried out by a method comprising comparing said profile to a good prognosis template and/or a poor prognosis template, wherein said good prognosis template comprises measurements of levels of transcripts of, or proteins encoded by, said

respective genes in said plurality of genes that are representative of levels of transcripts of, or proteins encoded by, said respective genes in a plurality of good outcome patients, and said poor prognosis template comprises measurements of levels of transcripts of, or proteins encoded by, said respective genes in said plurality of genes that are representative of levels of transcripts of, or proteins encoded by, said respective genes in a plurality of poor outcome patients, and wherein a good outcome patient is a breast cancer patient who has non-reoccurrence of metastases within a first period of time after initial diagnosis and a poor outcome patient is a breast cancer patient who has reoccurrence of metastases within a second period of time after initial diagnosis, and wherein:

(i) said individual is classified as having a good prognosis if said profile has a high similarity to said good prognosis template, has a low similarity to said poor prognosis template, or has a higher similarity to said good prognosis template than to said poor prognosis template, wherein said profile has a high similarity to said good prognosis template if the similarity to said good prognosis template is above a predetermined threshold, or has a low similarity to said poor prognosis template if the similarity to said poor prognosis template is below said predetermined threshold, or

(ii) said individual is classified as having a poor prognosis if said profile has a high similarity to said poor prognosis template, has a low similarity to said good prognosis template, or has a higher similarity to said poor prognosis template than to said good prognosis template, wherein said profile has a high similarity to said poor prognosis template if the similarity to said poor prognosis template is above said predetermined threshold, or has a low similarity to said good prognosis template if the similarity to said good prognosis template is below said predetermined threshold.

90. (Previously presented) A method for assigning a breast cancer patient to one of a plurality of categories in a clinical trial, comprising:

(a) determining if said person has a good prognosis or a poor prognosis using the method of claim 89; and

(b) assigning said patient to one category in a clinical trial if said patient is determined to have a good prognosis, and a different category if that patient is determined to have a poor prognosis.

91. (Canceled).

92. (Currently Amended) The method of ~~claim 91~~ claim 89, wherein said profile is an expression profile comprising measurements of said levels ~~a plurality~~ of transcripts ~~in a~~

~~sample derived from said patient~~, wherein said good prognosis template comprises measurements of ~~said plurality~~ levels of transcripts of said respective genes that are representative of expression levels of said transcripts in said plurality of good outcome patients, and wherein said poor prognosis template comprises measurements of ~~said plurality~~ levels of transcripts of said respective genes that are representative of expression levels of said transcripts in said plurality of poor outcome patients.

93. (Currently Amended) The method of claim 92, wherein measurement of each said transcript in said good prognosis template is an average of expression levels of said transcript in said plurality of good outcome patients, and wherein measurement of each said transcript in said poor prognosis template is an average of expression levels of said transcript in said plurality of poor outcome patients.

94. (Previously presented) The method of claim 89, wherein said ER/AGE is classified as high if said ER level is greater than $c\cdot(\text{AGE} - d)$, and wherein said ER/AGE is classified as low if said ER level is equal to or less than $c\cdot(\text{AGE} - d)$, wherein c is a coefficient, AGE is the age of said patient, and d is an age threshold.

95. (Previously presented) The method of claim 89, wherein said individual has been classified as ER^-, sporadic, and said plurality of genes comprises at least two of the genes for which markers are listed in Table 1.

96. (Previously presented) The method of claim 89, wherein said individual has been classified as ER^-, sporadic, and said plurality of genes comprises all of the genes for which markers are listed in Table 1.

97. (Previously presented) The method of claim 89, wherein said individual has been classified as ER^-, *BRCA1*, and said plurality of genes comprises at least two of the genes for which markers are listed in Table 2.

98. (Previously presented) The method of claim 89, wherein said individual has been classified as ER^-, *BRCA1*, and said plurality of genes comprises all of the genes for which markers are listed in Table 2.

99. (Previously presented) The method of claim 89, wherein said individual has been classified as ER+, ER/AGE high, and said plurality of genes comprises at least two of the genes for which markers are listed in Table 3.

100. (Previously presented) The method of claim 89, wherein said individual has been classified as ER+, ER/AGE high, and said plurality of genes comprises all of the genes for which markers are listed in Table 3.

101. (Previously presented) The method of claim 89, wherein said individual has been classified as ER+, ER/AGE low, LN+, and said plurality of genes comprises at least two of the genes for which markers are listed in Table 4.

102. (Previously presented) The method of claim 89, wherein said individual has been classified as ER+, ER/AGE low, LN+, and said plurality of genes comprises all of the genes for which markers are listed in Table 4.

103. (Previously presented) The method of claim 89, wherein said individual has been classified as ER+, ER/AGE low, LN^-, and said plurality of genes comprises at least two of the genes for which markers are listed in Table 5.

104. (Previously presented) The method of claim 89, wherein said individual has been classified as ER+, ER/AGE low, LN^-, and said plurality of genes comprises all of the genes for which markers are listed in Table 5.

105. (New) The method of claim 29, wherein said measurements of the levels of expression of said at least two respective genes in said good prognosis template is an average of expression levels of transcripts of said at least two respective genes in cell samples taken from said plurality of good outcome patients and wherein said measurements of the levels of expression of said at least two respective genes in said poor prognosis template is an average of expression levels of transcripts of said at least two respective genes in cell samples taken from said plurality of poor outcome patients.

REMARKS

Claims 1, 29, 42, 43, 45, 48, 54, 58-67, 73-74 and 88-104 are pending in the application. Claims 29, 42, 45, 48, 89, 92 and 93 have been amended to clarify the invention, and claim 105 has been added. Claims 1, 43, 73, 74, 88 and 91 have been cancelled without prejudice. Upon entry of this amendment, claims 29, 42, 45, 48, 54, 58-67, 89-90, and 92-105 will be pending.

Claim 29 has been amended to recite "an individual having breast cancer." Support for this amendments is found in the specification, *e.g.*, at page 16, paragraph [0053]; page 81, paragraph [00199] and page 83, paragraph [00203].

Claim 29 also has been amended to recite "wherein ER+ designates a high ER level and ER- designates a low ER level, wherein said ER/AGE is a metric of said ER level relative to the age of said individual, and wherein LN+ designates a greater than 0 lymph nodes status in said individual and LN- designates a 0 lymph nodes status in said individual." Support for this amendments is found in the specification, *e.g.*, at page 12, paragraph [0033] and page 91, paragraph [00225].

Claim 29 also has been amended to recite "determining for said individual a profile comprising measurements of the levels of expression of at least two respective genes." Support for this amendments is found in the specification, *e.g.*, at page 51, paragraph [00117] and page 55, paragraph [00123].

Claims 29, 42 and 89 have been amended to recite, in pertinent part, "comparing ... said profile to a good prognosis template and/or a poor prognosis template." Support for this amendment is found in the specification, *e.g.*, at page 13, paragraph [0034]; page 51, paragraph [00117]; and page 54, paragraph [00122].

Claims 29, 42 and 89 also have been amended to recite, in pertinent part, "having a good prognosis if said profile has a high similarity to said good prognosis template, has a low similarity to said poor prognosis template, or has a higher similarity to said good prognosis template than to said poor prognosis template, wherein said profile has a high similarity to said good prognosis template if the similarity to said good prognosis template is above a predetermined threshold, or has a low similarity to said poor prognosis template if the similarity to said poor prognosis template is below said predetermined threshold" and "having a poor prognosis if said profile has a high similarity to said poor prognosis template, has a low similarity to said good prognosis template, or has a higher similarity to said poor

prognosis template than to said good prognosis template, wherein said profile has a high similarity to said poor prognosis template if the similarity to said poor prognosis template is above said predetermined threshold, or has a low similarity to said good prognosis template if the similarity to said good prognosis template is below said predetermined threshold." Support for these amendments is found in the specification, *e.g.*, at page 13, paragraph [0034]; page 14, paragraph [0038]; page 19, paragraph [0070]; page 51, paragraph [00117]; page 54, paragraph [00122]; page 58, paragraph [00128] to page 60, paragraph [00132]; page 67, paragraph [00149]; and page 92, paragraph [00232].

Claim 29 also has been amended to recite, in pertinent part, "wherein said good prognosis template comprises measurements of the levels of expression of said at least two respective genes that are representative of levels of expression of said at least two respective genes in a plurality of good outcome patients and said poor prognosis template comprises measurements of the levels of expression of said at least two respective genes that are representative of levels of expression of said at least two respective genes in a plurality of poor outcome patients, and wherein a good outcome patient is a breast cancer patient who has non-reoccurrence of metastases within a first period of time after initial diagnosis and a poor outcome patient is a patient who has reoccurrence of metastases within a second period of time after initial diagnosis." Claims 42 and 89 also have been amended to recite, in pertinent part, "wherein said good prognosis template comprises measurements of levels of transcripts of, or proteins encoded by, respective genes in said plurality of genes that are representative of levels of transcripts of, or proteins encoded by, said genes in a plurality of good outcome patients and said poor prognosis template comprises measurements of levels of transcripts of, or proteins encoded by, respective genes in said plurality of genes that are representative of levels of transcripts of, or proteins encoded by, said genes in a plurality of poor outcome patients, and wherein a good outcome patient is a breast cancer patient who has non-reoccurrence of metastases within a first period of time after initial diagnosis and a poor outcome patient is a patient who has reoccurrence of metastases within a second period of time after initial diagnosis." Support for these amendments is found in the specification, *e.g.*, at page 51, paragraph [00117]; page 52, paragraph [00119]; page 54, paragraph [00122]; page 58, paragraph [00128]; and page 60, paragraph [00133].

Claim 45 has been amended to depend from claim 42, since claim 43 has been cancelled.

Claims 48 and 93 have been amended to recite "wherein measurement of each said transcript in said poor prognosis template is an average of expression levels of said transcript in said plurality of poor outcome patients." Support for this amendment is found in the specification, *e.g.*, at page 51, paragraph [00117] and page 60, paragraph [00133].

Claim 92 has been amended to depend from claim 89, since claim 91 has been cancelled.

Support for new claim 105 is found in the specification, *e.g.*, at page 13, paragraph [0035] and page 60, paragraph [00133].

No new matter has been added by these amendments.

I. STATEMENT OF THE SUBSTANCE OF THE OCTOBER 30, 2009 INTERVIEW WITH SUPERVISORY PATENT EXAMINER NGUYEN

Applicants thank Supervisory Patent Examiner ("SPE") Nguyen for the courtesies extended during the telephonic interview on October 30, 2009, with Applicant's representatives Adriane Antler and Sandra Brown (hereinafter "Interview I"). Pursuant to 37 C.F.R. § 1.133 and M.P.E.P. § 713.04, Applicants present this statement of the Substance of Interview I.

In Interview I, Applicants' representative Dr. Antler described to SPE Nguyen the following information regarding the Restriction Requirement. In February 2009, Examiner Martinell contacted Dr. Antler, informing her that he intended to issue a Restriction Requirement in the application, and asked if she would make an oral election of one of Groups I, II and III. Examiner Martinell also informed Dr. Antler that, if Group II or III was elected, he further required an election of an invention of one combination of genes. In response, Dr. Antler objected to the restriction to one combination of genes, explaining that (1) restricting the claims to one combination of genes would devalue the application, since the claims could readily be avoided by using genes presently within the scope of the claims that did not include the elected combination, (2) the full scope of the claims could not be practically recouped in divisional applications due to the enormous number of divisionals that would be necessitated, and (3) such a restriction is counter to the practice of the bioinformatics Group Art Unit 1631, which generally examined these types of claims without requiring such a restriction. Examiner Martinell stated that, if the claims of Group II were amended to recite "computer-implemented" and to specify the steps of the claims that are performed on a computer, he would withdraw the further requirement of the election of one combination of genes. Accordingly, a Second Preliminary Amendment Under 37 C.F.R. §

1.115 was filed on February 27, 2009, in which independent claims 29 and 42 were amended to specify the steps that are performed "on a computer" and new independent claim 89 was added which recited "computer-implemented" and specified the steps that are performed "on a computer." In July 2009, Examiner Martinell left a voicemail for Dr. Antler, informing her that he had changed his decision, and that he was would issue a written Restriction Requirement requiring the election of one combination of genes if Group II or III were elected. Subsequently, Applicants' representatives sought to contact Examiner Martinell to discuss the change in decision. The written Restriction Requirement was mailed on July 30, 2009. Subsequently, Applicants' representatives further discussed this matter with Examiner Martinell and with Marjorie Moran, SPE of Group Art Unit 1631.

SPE Nguyen advised Dr. Antler that he would discuss the Restriction Requirement with Examiner Martinell.

II. STATEMENT OF THE SUBSTANCE OF THE NOVEMBER 9, 2009 INTERVIEW WITH EXAMINER MARTINELL

Applicants thank Examiner Martinell for the courtesies extended during the telephonic interview on November 9, 2009, with Applicant's representative Adriane Antler (hereinafter "Interview II"). Pursuant to 37 C.F.R. § 1.133 and M.P.E.P. § 713.04, Applicants present this statement of the Substance of Interview II.

In Interview II, Examiner Martinell informed Applicant's representative Dr. Antler that he had discussed with SPE Moran the practice of Group Art Unit 1631 for examining bioinformatics claims such as the instantly pending claims. Dr. Antler pointed out to Examiner Martinell, by way of example, that the claims of U.S. Patent Nos. 7,171,311 B2 and 7,514,209 B2 are directed to methods that use the expression levels of genes selected from a table, without restriction to any particular gene or combination of genes from that table. Dr. Antler also noted to Examiner Martinell that the claims of U.S. Patent No. 7,514,209 B2 recite use of prognosis templates comprising the expression levels of genes selected from a table. Dr. Antler proposed that the instantly pending claims be amended to recite the use of prognosis templates, similar to the recitation in the claims of U.S. Patent No. 7,514,209 B2.[1] Examiner Martinell indicated that the proposed amendments would be considered favorably for withdrawing the requirement for selection of a combination of genes.

[1] These proposed claims amendments are made herein.

III. RESTRICTION REQUIREMENT

In the Office Action mailed August 19, 2009, the Examiner has required a restriction to one of the following three groups:

Group I. Claim 1, drawn to methods for identifying genes;

Group II. Claims 29, 42, 43, 45, 48, 54, 58-67 and 88-104, drawn to methods for classifying individuals by determining gene expression profiles; or

Group III. Claims 73 and 74, drawn to polynucleotide microarrays.

The Examiner contends that the above Groups are distinct inventions.

In response, Applicants hereby elect Group II, claims 29, 42, 43, 45, 48, 54, 58-67 and 88-104, drawn to methods for classifying individuals by determining gene expression profiles. Claim 105 is believed also to be in Group II.

Additionally, the Examiner has required a selection of one combination of genes for examination. (Office Action at paragraph bridging pages 2-3.) In order to be fully responsive, Applicants hereby provisionally elect, with traverse, the combination of genes corresponding to the following markers selected from Tables 1-5:

Table	Accession/Contig No.	Gene	SEQ ID
Table 1	NM_000599	IGFBP5	51
	NM_002205	ITGA5	93

Table	Accession/Contig No.	Gene	SEQ ID
Table 2	NM_002888	RARRES1	109
	NM_005218	DEFB1	177

Table	Accession/Contig No.	Gene	SEQ ID
Table 3	NM_003158	STK6	113
	NM_007019	UBCH10	217

Table	Accession/Contig No.	Gene	SEQ ID
Table 4	NM_002038	G1P3	85
	NM_005101	ISG15	169

Table	Accession/Contig No.	Gene	SEQ ID
Table 5	NM_006096	NDRG1	199
	NM_004207	SLC16A3	139

The Examiner also has required "identification of the claims encompassing the elected invention." (Office Action at page 3, first full paragraph.) The pending claims believed to be readable on this selected combination of genes are claims 29, 42, 45, 48, 54, 58-67, 89, 90 and 92-105.

With respect to the requirement for selection of one combination of genes, Applicants respectfully traverse. To restrict the claims to one combination of genes would destroy the value of the invention and would be inconsistent with the practice of Group Art Unit 1631, the art unit that examines bioinformatics claims such as the instant ones.

The restriction to one combination of genes would destroy the value of the invention, because the full scope of the claims could not be readily or practically recouped in divisional applications. Indeed, the requirement to make such an election unduly narrows the claimed invention so as to permanently restrict claim scope for reasons unrelated to patentability. In order to recover the full scope of claim 1 as pending, in view of the restriction requirement, Applicants would have to file millions of divisional applications to cover all possible combinations, which is clearly impractical due, *inter alia*, to cost considerations. In particular, the claims of any given patent that matures from an application restricted to one combination of genes could be easily circumvented by simply substituting one of the genes in the selected combination with another of the genes from Tables 1-5.[2]

Furthermore, such a requirement for restriction to one combination of genes would be inconsistent with the practice of Group Art Unit 1631. As Dr. Antler pointed out to Examiner Martinell, the claims of U.S. Patent Nos. 7,171,311 B2 and 7,514,209 B2 (both examined in Group Art Unit 1631) are directed to prognostic-related methods that use the expression levels of at least 5 genes selected from a list of genes in a table, without restriction to any particular gene or combination of genes from that table. Indeed, the genes listed in Tables 1-5 of the instant application were selected ***because*** each of them is informative for a breast cancer patient's prognosis to a greater degree than would be expected by chance. (See instant specification at page 20, paragraph [0072]; page 25, paragraph [0087]; page 26, paragraph [0091] to page 28, paragraph [00100]; and page 93, paragraph [00235].) Thus, as has already been done in the examination of U.S. Patent Nos. 7,171,311 and 7,514,209, the claims should

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[2] Indeed, in the prosecution of an analogous case, U.S. Patent No. 7,514,209, a Declaration under 37 C.F.R. § 1.132 was filed showing that one thousand (1,000) different combinations of five (5) genes, randomly selected from a table containing 231 gene markers, could each be used to achieve a successful classification of a patient as to prognosis according to the claimed method.

be examined consistent with the practice of bioinformatics Group Art Unit 1631, without restriction to any given combination of genes.

Accordingly, Applicants respectfully traverse the further requirement for restriction to one combination of genes and hereby retain the right to petition from the restriction requirement under 37 C.F.R. § 1.144. Applicants submit that examination of the claims as pending, without restriction to one combination of genes, would not be a serious burden on the Examiner. The Manual of Patent Examining Procedure (MPEP) § 803 states:

> [i]f the search and examination of **>all the claims in an< application can be made without serious burden, the examiner must examine *>them< on the merits, even though **>they include< claims to independent or distinct inventions.

(MPEP § 803, Eighth Edition, Rev. 7, July 2008 at page 800-4).

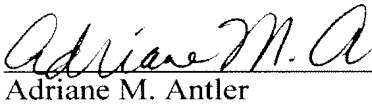
In view of the foregoing, Applicants respectfully request withdrawal of the further requirement for restriction to one combination of genes.

CONCLUSION

Entry and consideration of the above amendments and remarks are respectfully requested.

Respectfully submitted,

Date: December 15, 2009



32,605 (Reg. No.)

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